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Review

Limbic thalamus and state-dependent behavior: The paraventricular nucleus of the thalamic midline as a node in circadian timing and sleep/wake-regulatory networks

Valeria Colavito, Chiara Tesoriero, Amenu T. Wirtu, Gigliola Grassi-Zucconi, Marina Bentivoglio*

Department of Neurological and Movement Sciences, University of Verona, Italy

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ABSTRACT

The paraventricular thalamic nucleus (PVT), the main component of the dorsal thalamic midline, receives multiple inputs from the brain stem and hypothalamus, and targets the medial prefrontal cortex, nucleus accumbens and amygdala. PVT has been implicated in several functions, especially adaptation to chronic stress, addiction behaviors and reward, mood, emotion. We here focus on the wiring and neuronal properties linking PVT with circadian timing and sleep/wake regulation, and their behavioral implications. PVT is interconnected with the master circadian pacemaker, the hypothalamic suprachiasmatic nucleus, receives direct and indirect photic input, is densely innervated by orexinergic neurons which play a key role in arousal and state transitions. Endowed with prominent wake-related Fos expression which is suppressed by sleep, and with intrinsic neuronal properties showing a diurnal oscillation unique in the thalamus, PVT could represent a station of interaction of thalamic and hypothalamic sleep/wake-regulatory mechanisms. PVT could thus play a strategic task by funneling into limbic and limbic-related targets circadian timing and state-dependent behavior information, tailoring it for cognitive performance and motivated behaviors.

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* Corresponding author at: Department of Neurological and Movement Sciences, School of Medicine, Strada Le Grazie 8, 37134 Verona, Italy. Tel.: +39 045 8027155; fax: +39 045 8027163.
E-mail address: marina.bentivoglio@univr.it (M. Bentivoglio).

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1. Introduction

The midline nuclei of the thalamus have received in the last years sudden, unprecedented attention as substrates of cognitive functions, as well as mood, emotions, and reward (e.g. Hamlin et al., 2009; Price and Drevets, 2010; Saalmann, 2014; Sengupta and McNally, 2014; Varela, 2014). This may seem surprising given that the midline nuclei, together with the intralaminar nuclei, have historically represented the core of the "nonspecific thalamus", involved in a general role of diffuse activation of the cortical mantle.

Furthermore, on the basis of studies in different species and with different methodological approaches, a functional subdivision between the dorsal and ventral groups of the midline thalamic nuclei seems to be currently delineated. Thus, data indicate that cell groups of the ventral thalamic midline are implicated in memory processes (e.g. Cassel et al., 2013; Vertes, 2006; Xu and Südhof, 2013). On the other hand, the dorsal thalamic midline, whose main component is the paraventricular nucleus of the thalamus (PVT), has been implicated in the response to psychoactive drugs (Cohen et al., 1998; Deutch et al., 1995, 1998), adaptation to stressful conditions, modulation of viscerosensory stimuli, positive and negative emotional states, drug-seeking and reward mechanisms (e.g. James and Dayas, 2013; Martin-Fardon and Boutrel, 2012; Hsu et al., 2014; Sengupta and McNally, 2014).

Other sets of findings indicate that neurons of the dorsal thalamic midline, and especially PVT neurons, could play a role in the modulation of state-dependent behavior. We here focus on this aspect, to discuss the neural and functional links of the dorsal thalamic midline with circadian timing and sleep/wake regulation, in which all behavioral performances are inscribed.

1.1. From the "nonspecific thalamus" to the "midline and intralaminar thalamus"

The subdivision of thalamic nuclei into the broad categories of "specific" and "nonspecific" nuclei dates back several decades, to the beginning of the modern era of neurophysiology and neuroanatomy, which was then based on anterograde and degeneration techniques for the study of neuronal connections. The functional properties and organization of neural circuits was subsequently re-examined with the advent of single unit recording and tract tracing based on the anterograde and retrograde axonal transport of tracers. A treatise on the itinerary of knowledge on the different categories of thalamic nuclei goes beyond the limits and scope of the present review. It is, however, of interest that this matter is still debated.

The concept of "nonspecific" thalamus, as well as the designation of the midline nuclei as "nonspecific" (see Bentivoglio et al., 1991), originated from different sets of data. We will here mention only two of them. So-called recruiting responses were recorded over a large cortical expanse after low frequency stimulation of thalamic domains in the cat, which included the intralaminar nuclei and, at the midline, the nucleus reuniens and the rhomboid nucleus (Morison and Dempsey, 1942). Furthermore, The diffuse projections, widely distributed upon different cortical areas, were supposed to derive from these "nonspecific" thalamic nuclei (see Jones, 2007; Macchi et al., 1996). The medial core of the "nonspecific" thalamus was thus viewed as the collector transmitting upon the cortical mantle the activation conveyed from the brain stem through the ascending arousal system electrophysiologically identified by Moruzzi and Magoun (1949). While a diffuse thalamocortical system seemed to have been delineated, such "cinderella-like diffuse projection system" (Jasper, 1949) seemed to perform less "elegant" and punctual operations than those of the "specific" thalamic relay nuclei. Altogether, however, this view emphasized a role of medial thalamic cell groups in what would be defined nowadays as state-dependent behavior.

The "nonspecificity" of the "nonspecific" thalamus was challenged in the 1990s on the basis of data accumulated in the meantime, including the definition of discrete, rather than diffuse, cortical targets (e.g. Bentivoglio et al., 1991; Groenewegen and Berendse, 1994; Macchi and Bentivoglio, 1999). Novel views were developed. The concept and anatomical organization of the brain stem reticular formation were revised on the basis of the discovery of monoaminergic systems. Even the role of the reticulo-thalamocortical pathway in arousal has been recently reconsidered (Fuller et al., 2010). Thalamic nuclei were subdivided into "first order" and "higher order" nuclei on the basis of their driving input (Guillery, 1995; Guillery and Sherman, 2002). Thalamocortical neurons were subdivided into "core" ("specific"), and "matrix" ("nonspecific") neurons, distributed in different thalamic nuclei, as key players in the synchrony of cortical activity (Jones, 2001, 2007).

One of the results of this wealth of data and of the relevant theoretical debates is the recent, frequent "upgrading" of the "nonspecific" medial thalamus to the cautious, topographical designation of "midline and intralaminar nuclei" (e.g. Benarroch, 2008; Sengupta and McNally, 2014; Van der Werf et al., 2002; Varela, 2014). It remains that these cell groups differ from sensory and motor relay nuclei of the dorsal thalamus in their effect on sleep and arousal, function in cognitive tasks, mechanisms of temporal synchronization and temporal binding in the cerebral cortex (e.g. Benarroch, 2008; Llinás et al., 2002; Llinás and Steriade, 2006; Van der Werf et al., 2002). Concerning the cortical targets, given that all thalamic nuclei reach more than one cortical area (Jones, 2007; Macchi et al., 1996), the concept of diffuse thalamocortical projections was revised, and the task of a diffuse cortical innervation was passed on to aminergic systems, and, more recently also to orexinergic innervation (see Section 3.4). Solidly grounded is instead the concept of the midline and intralaminar nuclei as source of thalamic output to the striatal complex. In addition, as dealt with below, it has been assessed that the midline nuclei are the source of thalamic output to limbic and limbic-related targets.

2. The modest puzzle of the thalamic midline

Relatively small in rodents, relatively small and thin in non-human primates and humans, partitioned into cell groups traversed by fibers with a variety of neurochemical phenotypes (how many do terminate there or are simply passing by?), the collection of cell groups located along the midline of the thalamus appears as an unassuming "puzzle" among the midline structures of the cerebral hemispheres. In the human brain, in which the third ventricle may completely divide the two halves of the thalamus when the massa intermedia is absent, the midline nuclei are located on each side along the ventricle.

The midline thalamic nuclei are composed dorsally by PVT (Pa in the abbreviations used in Olszewski's nomenclature of the macaque thalamus; Olszewski, 1952) and the paratenial and intermediodorsal nuclei, and ventrally by the rhomboid nucleus and the nucleus

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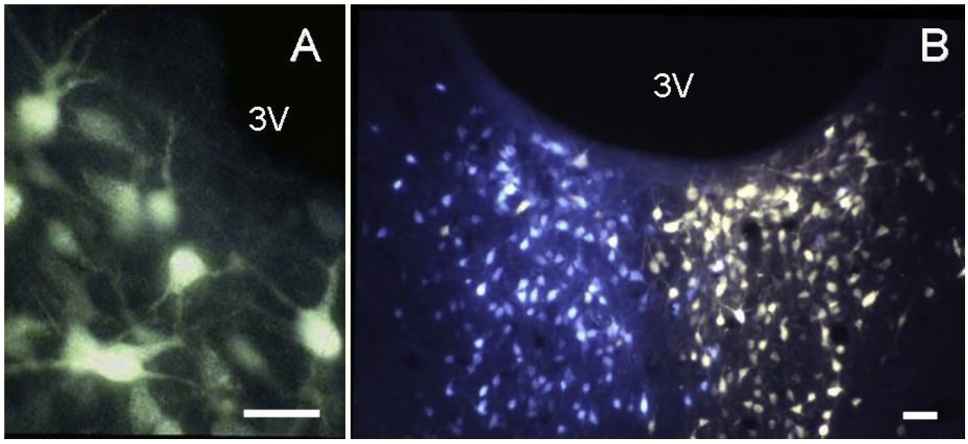

Fig. 1. The plate shows neurons retrogradely labeled in the anterior paraventricular thalamic nucleus of the rat after injection of the fluorescent tracers FluoroGold (A and B, right side) or Fast Blue (B, left side) in the amygdala. Note the high density of these neurons. Note in A labeled dendrites extending toward the ependymal surface. 3V, third ventricle (images from the laboratory archival material). Scale bars: 50 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

reuniens. PVT, located between the habenulae, was considered part of the epithalamus, together with the habenulae and the pretectal nuclei, on the basis of early developmental findings in the rabbit (Rose, 1942) and indications of lack of projections to the cerebral cortex (see Bentivoglio et al., 1991). However, PVT shares chronological developmental gradients with the other midline thalamic nuclei and, more in general, with the nuclei of the dorsal thalamus (Altman and Bayer, 1979). Furthermore, it was assessed that PVT contributes to the thalamocortical system with its output to the cerebral cortex (see Section 2.2).

PVT (whose fame was obscured for decades by that of its hypothalamic homonym, the paraventricular nucleus of the hypothalamus) extends throughout the anteroposterior extent of the thalamus, lining the third ventricle. The paratenial nucleus borders laterally PVT in its anterior third. Located in the human thalamus in the dorsomedial strip of tissue, devoid of myelin, which borders the ventricle (Uroz et al., 2004), PVT appears to be one of the most stable thalamic structures, in terms of topographical location and relative size, throughout mammalian evolution (Bentivoglio et al., 1991; Van der Werf et al., 2002). It has been observed in the rat that at the ventricular surface PVT neurons extend dendrites toward the ependymal layer (Fig. 1A). Ultrastructural investigations have shown that PVT dendritic arborizations are separated from the ependyma by thin astrocytic processes, establishing a specialized relationship with ependymal cells (Balercia et al., 1992; Bentivoglio et al., 1991).

Neurons of PVT are excitatory and utilize excitatory amino acids as neurotransmitters (Frassoni et al., 1997). Concerning calcium-binding proteins, calbindin D28k-containing neurons are distributed in the rat midline thalamic nuclei (Arai et al., 1994; Battaglia et al., 1992; Celio, 1990; Frassoni et al., 1997). However, PVT neurons are especially characterized by calretinin expression in rodents (Arai et al., 1994; Winsky et al., 1992; Fig. 2), monkey (Fortin et al., 1996), and humans (Fortin et al., 1998; Uroz et al., 2004).

In the rat and the mouse, PVT, as other nuclei of the rodent dorsal thalamus, does not contain interneurons, which in carnivores and primates represent a subpopulation of GABAergic inhibitory local circuit neurons throughout the dorsal thalamus (Arcelli et al., 1997). The reticular thalamic nucleus (Rt), the sheet of GABAergic neurons of the ventral thalamus which surrounds the dorsal thalamus, sends inhibitory efferents to the nuclei of the dorsal thalamus. This relationship is reciprocal since thalamic fibers emit collaterals to Rt in their thalamofugal pathways (Jones, 2007). As reported in the rat, innervation of the midline nuclei originates from the medial portion of the rostral pole of Rt (Cornwall and Phillipson, 1988; Kolmac and Mitrofanis, 1997), including cells, located ventromedially in Rt, which innervate PVT (Li and Kirouac, 2012).

2.1. Inputs: the busy corridor of the thalamic midline

Afferents to PVT have been extensively investigated in the rat and in the monkey (e.g. Chen and Su, 1990; Hsu and Price, 2009; Krout et al., 2002; Li and Kirouac, 2008, 2012; Moga et al., 1995; Otake et al., 1994; Vertes and Hoover, 2008), and are here summarized. Concerning subcortical inputs, it should be recalled that PVT is densely innervated by cells distributed in several centers of the brain stem and hypothalamus. In addition to the monoaminergic input (see below), PVT receives from the brain stem input from the nucleus of the solitary tract, the parabrachial nuclei and the

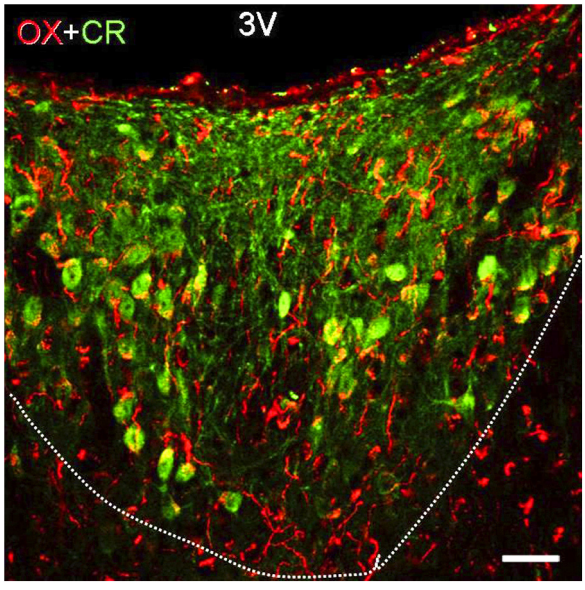

Fig. 2. Confocal microscopy image showing orexin-A-immunoreactive (OX, red) preterminal and terminal fibers innervating in the rat paraventricular thalamic nucleus, whose boundaries are indicated by the dotted line. Neurons are labeled by calretinin (CR, green) immunoreactivity, which is prominently expressed by neurons of the paraventricular thalamic nucleus. Note the dense plexus of preterminal and terminal orexinergic fibers, which also show a perisomatic distribution. 3V, third ventricle. Scale bar: 50 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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periaqueductal gray (Krout and Loewy, 2000a,b; Krout et al., 2002; Li and Kirouac, 2012). A limited input deriving from the deep layers of the superior colliculus was also reported (Krout et al., 2001). In the rat, contingents of cortical and subcortical fibers which innervate PVT send collaterals to the nucleus of the solitary tract, a feature that has been implicated in the simultaneous modulation of visceral reflex excitability and thalamocortical activity (Otake et al., 1994). The midline nuclei, including PVT, also receive spinothalamic tract fibers (see Bentivoglio et al., 1991).

As noted by Li and Kirouac (2008), the abundance of direct input from several hypothalamic areas is a distinctive feature of PVT among the midline nuclei and, more in general, among other thalamic domains. The links with the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, are dealt with in Section 3.1, and PVT innervation from orexinergic neurons of the perifornical/lateral hypothalamus is dealt with in Section 3.5. PVT is also linked to many other hypothalamic cell groups by afferents deriving from the subparaventricular zone in the rat (Moga et al., 1995; Watts and Swanson, 1987; Watts et al., 1987) and hamster (Morin et al., 1994), from the medial preoptic area, dorsomedial, ventromedial and arcuate nuclei in the rat (Canteras et al., 1994; Li and Kirouac, 2012; Moga et al., 1995) and in the monkey (Hsu and Price, 2009).

The neurons which project to PVT from the dorsomedial nucleus of the hypothalamus, a key area for the regulation of circadian rhythms (Saper, 2013; see Section 3.1), include neurons responsive to leptin (Gautron et al., 2010), the adipocyte hormone currently at the center stage in the regulation of metabolism, energy homeostasis and neuroendocrine functions (e.g. Park and Ahima, 2014; Stieg et al., 2014).

A distinctive feature of the subcortical input to the thalamic midline, and in particular to PVT, is also the large variety of chemically characterized fibers, documented in many species including non-human primates and humans. Thus, PVT receives a dense aminergic innervation from the brain stem: adrenergic innervation from the medulla oblongata (Otake and Ruggiero, 1995; Phillipson and Bohn, 1994), noradrenergic fibers from the locus coeruleus (Jones and Yang, 1985; Krout et al., 2002; Vogt et al., 2008), serotonergic innervation from the median and dorsal raphe (Cropper et al., 1984; de Medeiros Silva et al., 2014; Hsu and Price, 2009; Otake and Ruggiero, 1995; Vertes et al., 2010), dopaminergic fibers which derive primarily from cells of the periventricular and posterior hypothalamic areas (García-Cabezas et al., 2007, 2009; Hökfelt et al., 1976; Otake and Ruggiero, 1995; Takada et al., 1990). The aminergic innervation of PVT includes histaminergic fibers deriving from the tuberomammillary nucleus of the posterior hypothalamus (Airaksinen and Panula, 1988; Airaksinen et al., 1989; Jin et al., 2002; Panula et al., 1989). PVT is sparsely innervated by cholinergic fibers which originate from the mesopontine tegmentum (Heckers et al., 1992; Otake and Ruggiero, 1995). All these fiber systems are distributed also to other thalamic domains.

Peculiar of the thalamic midline is a remarkable array of peptidergic fiber systems, originating mostly from hypothalamic cell groups. These contain, for example, Leu-enkephalin (Battaglia et al., 1992; Uroz et al., 2004); endomorphin (Pierce and Wessendorf, 2000); somatostatin (Molinari et al., 1987); substance P (Battaglia et al., 1992; Molinari et al., 1987; Uroz et al., 2004), deriving in the rat from the brain stem (Otake, 2005); cholecystokinin (Battaglia et al., 1992; Molinari et al., 1987; Otake, 2005), deriving in the rat from the periaqueductal gray, dorsal raphe and dorsomedial nucleus of the hypothalamus (Otake, 2005); neuropeptide Y (Freedman and Cassell, 1994; Kampe et al., 2009; Molinari et al., 1987); corticotropin-releasing hormone (Hsu and Price, 2009); thyrotropin-releasing hormone (Merchenthaler et al., 1988; Wittmann et al., 2009); cocaine and amphetamine-related transcript (CART), which derive from hypothalamic cell groups including the dorsomedial nucleus (Kampe et al., 2009; Kirouac et al., 2006; Parsons et al., 2006); gastrin-releasing peptide (GRP) (Hermes et al., 2013), vasoactive intestinal polypeptide (VIP) and arginine-vasopressin (AVP), which derive from the SCN (Freedman and Cassell, 1994; Novak et al., 2000a; Watts and Swanson, 1987; see Section 3.1). As mentioned above, fibers deriving from orexin-containing neurons have been added in recent years to the long list of peptidergic innervation of the thalamic midline (see Section 3.5). Neurotensin-containing innervation of the thalamic midline, concentrated in the rat in PVT (Jennes et al., 1982; Makino et al., 1987; Watts and Swanson, 1987), could be of renewed interest in view of the co-expression of neurotensin in hypothalamic orexin-containing neurons (see Section 3.5), as reported in the mouse (Furutani et al., 2013).

Most of these systems distribute on their way axon terminals to midline thalamic cell groups and terminate then in PVT. Some of the fiber contingents, such as, for example, AVP fibers, target only the dorsal thalamic midline, being concentrated in PVT.

Peptide release, which in general modulates the fast synaptic activity due to the synaptic release of excitatory glutamate or inhibitory GABA (van den Pol, 2012), has been implicated in the regulation of the intrinsic neuronal properties in PVT (see Section 5). Peptidergic innervation of PVT has been implicated in different functions. For example, cholecystokinin innervation of PVT has been related to the adaptation to chronic stress and regulation of the hypothalamic–pituitary–adrenal axis (Bhatnagar et al., 2000).

Of note, many of the chemically characterized fiber systems which innervate PVT, including noradrenergic and serotonergic fibers from the brain stem, as well as histaminergic, orexinergic and neurotensin-containing fibers from the hypothalamus, are part of the sleep/wake-regulatory networks (Berridge et al., 2012; Brown et al., 2012; Furutani et al., 2013; Jones, 2005; Pace-Shott and Hobson, 2002; see Section 3.4).

Of interest is also the finding that PVT contains neuron clusters and high density of neuropil expressing the neuronal isoform of nitric oxide synthase, the synthetic enzyme of the gaseous free radical nitric oxide. Nitric oxide synthase-containing neurons and fibers have a discrete distribution in the thalamus including, along the midline, the rhomboid and central medial nuclei (Bertini and Bentivoglio, 1997; Otake and Ruggiero, 1995). Extrinsic nitric oxide synthase innervation of PVT derives from cells of the mesopontine tegmentum (and predominantly from noncholinergic neurons in this area), as well as hypothalamic neurons (Otake and Ruggiero, 1995). Nitric oxide dampens the intrinsic oscillatory activity of thalamocortical neurons *in vitro* (Pape and Mager, 1992). Extracellular nitric oxide concentration in the thalamus is high during wakefulness and rapid eye movement (REM) sleep and decreases during slow wave sleep (see Section 3.4), suggesting a role of nitric oxide production in the thalamus in arousal (Williams et al., 1997), Most evidence, based also on the inducible isoform of nitric oxide synthase, suggests, however, that nitric oxide promotes slow-wave sleep (Brown et al., 2012; Coulon et al., 2012).

The possible occurrence of intrathalamic connections within the midline is an interesting aspect which would require further investigation. As a general organizational principle, intrathalamic crosstalk is mediated by Rt, with no direct connections between the nuclei of the dorsal thalamus (Jones, 2007). However, interconnections of the midline thalamic nuclei were mentioned in the rat (Van der Werf et al., 2002; Vertes and Hoover, 2008). The existence of these connections would open a novel scenario of crosstalk between the dorsal and ventral groups of midline thalamic nuclei.

Among forebrain sources, PVT receives input from basal forebrain neurons (Kolmac and Mitrofanis, 1999), the bed nucleus of the stria terminalis and the central nucleus of the amygdala (Li and Kirouac, 2012; Reardon and Mitrofanis, 2000).

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Cortical input to PVT in the rat derives from the medial prefrontal cortex as well as from the hippocampal subiculum (Li and Kirouac, 2012; Vertes, 2002). The medial prefrontal cortex includes four main divisions (medial agranular, anterior cingulate, prelimbic and infralimbic cortices) and is homologous to the dorsolateral prefrontal cortex of primates (see Vertes, 2002). PVT receives input especially from the prelimbic, infralimbic and agranular insular cortices.

2.2. Outputs to multiple targets

The efferents of the thalamic midline reach limbic and limbic-related targets: the nucleus accumbens, which is the limbic portion of the striatal complex; the hippocampus, which is main target of the efferents of the ventral thalamic midline and in particular of the nucleus reuniens (Herkenham, 1978; Vertes et al., 2006); the amygdala, which is a main target of the dorsal thalamic midline and in particular, as mentioned below, of PVT. The midline nuclei are therefore a main component of the "limbic thalamus" (Bentivoglio et al., 1993).

A comprehensive study of the efferents of PVT and the adjacent paratenial nucleus of the rat has emphasized that these nuclei "appear critical for routing visceral/emotional information to structures of the limbic forebrain, including the limbic cortex, in the control of goal-directed behaviors" (Vertes and Hoover, 2008). Thus, in the rat the cortical output of PVT is concentrated in the medial prefrontal cortex, and also reaches the entorhinal and perirhinal cortices and the subiculum of the hippocampus (Berendse and Groenewegen, 1991; Hoover and Vertes, 2007; Moga et al., 1995; Su and Bentivoglio, 1990; Van der Werf et al., 2002; Vertes and Hoover, 2008). The densest terminal fields of PVT axons are in the infralimbic and prelimbic cortices, as shown by anterograde and retrograde tracing (Hoover and Vertes, 2007; Moga et al., 1995; Vertes and Hoover, 2008). PVT also projects to the lateral septum, anterior olfactory nucleus and olfactory tubercle (Moga et al., 1995; Vertes and Hoover, 2008). In the macaque monkey, PVT is primarily connected with perigenual areas on the medial surface of the frontal lobe, part of the "medial prefrontal network" (Hsu and Price, 2007, 2009).

The midline thalamic nuclei, including PVT, contribute to the thalamostriatal system (Jones, 2007). PVT projects in the rat to the dorsal striatum, but its main target in the striatal complex is the nucleus accumbens (Berendse and Groenewegen, 1991; Erro et al., 2002; Moga et al., 1995; Vertes and Hoover, 2008; Su and Bentivoglio, 1990) which is the key center for reward mechanisms (e.g. Kelley et al., 2005; Peciña et al., 2006; Richard et al., 2013), PVT fibers terminate both in the core and the shell of the nucleus accumbens, with dense terminal fields in the latter, as described in the rat and the monkey (e.g. Berendse and Groenewegen, 1990; Hsu and Price, 2009; Li and Kirouac, 2008; Moga et al., 1995; Vertes and Hoover, 2008). Glutamate released from PVT terminals modulates dopamine release in the nucleus accumbens (Parsons et al., 2007). In the rat, dopaminergic fibers and PVT axons show frequent convergence on the same neurons in the shell of the nucleus accumbens, an association that was not found in the prefrontal cortex (Pinto et al., 2003).

PVT projects densely to the amygdaloid complex, especially the central and basal nuclei, as well as to the bed nucleus of stria terminalis and other components of the extended amygdala (Hsu and Price, 2009; Li and Kirouac, 2008; Moga et al., 1995; Turner and Herkenham, 1991; Vertes and Hoover, 2008). In the rat, neurons projecting to the amygdala are very numerous in the dorsal part of PVT reaching the ventricular surface (Fig. 1B).

The broad input to PVT deriving from hypothalamic cell groups is reciprocated by sparse descending efferents, which include fibers distributed to the paraventricular, dorsomedial, ventromedial and arcuate hypothalamic nuclei, as well as to the medial preoptic and perifornical areas (Csáki et al., 2000; Hsu and Price, 2009; Li and Kirouac, 2008; Marchant et al., 2010; Moga et al., 1995; Vertes and Hoover, 2008), besides the SCN (see Section 3.1).

2.3. The paraventricular thalamic nucleus as an "interface"

The term "relay" is in general used to define the thalamic cell groups which receive, process and transfer information. It is interesting to note that in many instances PVT is instead referred to as an "interface". According to the Oxford Dictionary, "interface" means "a point where two systems, subjects, organizations, etc. meet and interact" (or, in computing "a device or program enabling a user to communicate with a computer"). The "relay" as electrical device is instead "activated by a current or signal in one circuit to open or close another circuit" (www.oxforddictionaries.com). The distinctive feature of an interface is therefore its action on multiple circuits.

PVT is frequently and explicitly referred to as an interface due to its potential role as a node linking different functional systems. For example, it has been proposed that PVT provides an interface between incoming signals related to arousal, including visceral arousal, food reward, circadian control, and outflow to the striatal complex, and therefore motor output pathways (Kelley et al., 2005; Parsons et al., 2006). It has also been proposed that PVT acts as an interface between sensory inputs and limbic and cortical structures of the extended amygdala (Heydendael et al., 2011) and, as dealt with below, an interface between the biological clock "and other regions of the brain" (Vertes and Hoover, 2008). Which is the role of PVT as multifaceted interface between different systems?

3. The network linking the paraventricular thalamic nucleus with the circadian pacemaker and the orexinergic system

3.1. The paraventricular thalamic nucleus and circadian timekeeping

The SCN, a dense collection of neurons lying bilaterally on the optic chiasm in the anterior hypothalamus, is the dominant circadian pacemaker in the mammalian brain (Dibner et al., 2010; Golombek and Rosenstein, 2010; Morin and Allen, 2006). Hierarchically at the top of the circadian timing system, the SCN synchronizes endogenous biological rhythms throughout the 24 h of the day (*circa diem*).

The SCN is entrained by photic and non-photic stimuli (Dibner et al., 2010; Golombek and Rosenstein, 2010; Morin and Allen, 2006). Light levels in the environment provide the main synchronizer for the SCN, which is an essential adaptive feature. This input derives from intrinsically photosensitive retinal ganglion cells which contain the photopigment melanopsin. Photic information is conveyed bilaterally to the SCN through retinohypothalamic tract fibers, which utilize glutamate as neurotransmitter. In the rat, retinal fibers are concentrated in the ventrolateral portion of the SCN, the so-called core of the nucleus, and this distribution has species-related variations, as documented in the mouse and in the hamster (Morin, 2013; Morin and Allen, 2006). Neurons of the SCN are GABAergic and their chemical signature includes colocalization of GABA with different peptides. The SCN core contains VIP- and GRP-immunoreactive neurons. The dorsomedial portion, the so-called shell of the SCN, contains a large population of AVP-immunoreactive neurons (Antle and Silver, 2005; Golombek and Rosenstein, 2010).

Neural circuits, and possibly also humoral, diffusible signals (Ralph et al., 1990; Silver et al., 1996; Tousson and Meissl, 2004)

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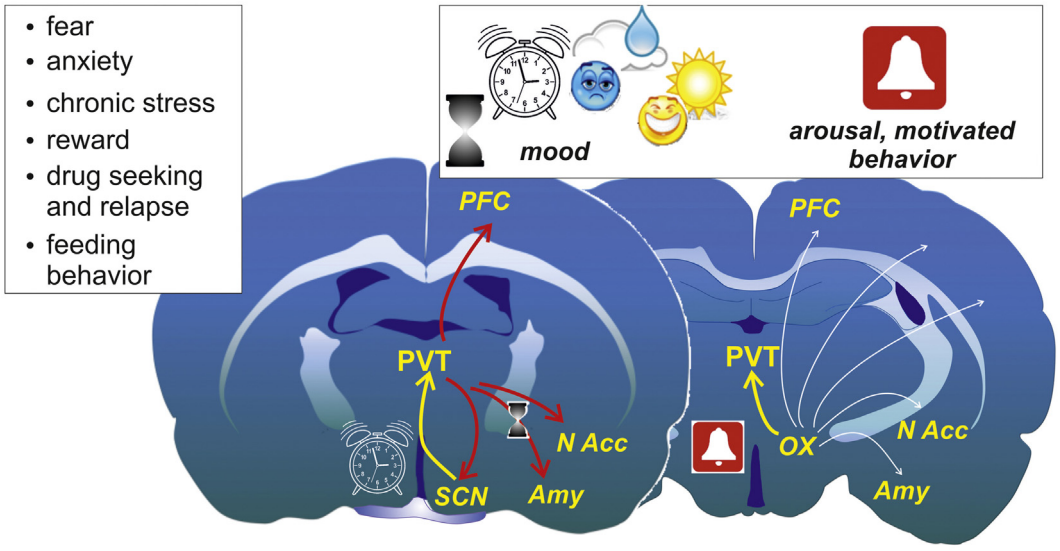

Fig. 3. Sketches summarizing circadian timing and orexinergic circuits in which the paraventricular thalamic nucleus (PVT) is inserted and their implications in emotional and motivational aspects of behavior and stress adaptation. (Left panel) Input from the biological clock, the suprachiasmatic nucleus (SCN), which is reciprocated, is transferred through PVT to its targets (PFC, medial prefrontal cortex; N Acc, nucleus accumbens; Amy, amygdala and extended amygdala), as demonstrated for PVT neurons projecting to the amygdala (Peng and Bentivoglio, 2004). Circadian timing information, linked to environmental light information (conveyed to PVT indirectly through the SCN and the intergeniculate leaflet, and directly via retinal fibers), and funneled through PVT into the limbic system, can thus play a role in mood and affect regulation related also to environmental influence. (Right panel) Efferents of orexin (OX)-containing neurons of the lateral hypothalamus, which play a key role in arousal, behavioral state transition, and motivational drive, are concentrated in the thalamus in PVT, and sparsely innervate the cerebral cortex (including the medial prefrontal cortex), the nucleus accumbens and the amygdala, which are also direct targets of the PVT outputs. The orexinergic innervation of PVT, which is excitatory and could amplify cortical activation, could be crucial in vigilance and arousal functions needed for the integrative action played by PVT in many functions, including the adaptation to chronic stress.

have been implicated in the SCN regulation of endogenous biological rhythms, which include the rest/activity cycle, the sleep/wake cycle, metabolic cycles, and hormonal secretion. The direct output of the SCN is, however, remarkably limited, indicating that circadian timing information is routed through indirect, polysynaptic pathways to the neural centers of control of different endogenous rhythms (Saper, 2013). It has been proposed that such multistep regulation could allow "flexibility in organizing daily schedules" (Saper et al., 2005a).

The densest output of the SCN thus reaches nearby hypothalamic targets, namely the subparaventricular zone and dorsomedial nucleus of the hypothalamus. These regions then transmit information on circadian timing to other cell groups, including those involved in sleep/wake regulation (Deurveilher and Semba, 2005; Saper, 2013; Saper et al., 2005b). Of special interest in the present context is that, as mentioned above (see Section 2.1), PVT is among the targets of the efferents of the subparaventricular zone and dorsomedial hypothalamic nucleus.

Some SCN fibers reach more distant targets. Interestingly, the PVT is recipient of probably the densest extrahypothalamic, direct SCN output. Circadian timing information transmitted by the SCN reaches, therefore, PVT both indirectly and directly.

In the rat, the SCN innervation of PVT was initially reported as relatively sparse and seemed to derive mainly from an area of the medial preoptic nucleus dorsal to the SCN (Watts et al., 1987). However, with sensitive retrograde tract tracing approaches (Chen and Su, 1990; Leak and Moore, 2001; Watts and Swanson, 1987), numerous SCN neurons, located in the shell of the nucleus, were found to project in the rat to PVT. Dense SCN projections to PVT were found in the hamster (Kalsbeek et al., 1993). The SCN-PVT connection has been verified in both nocturnal and diurnal rodents (Novak et al., 2000a), in the macaque monkey (Hsu and Price, 2009), as well as in the human brain by *post-mortem* tracing (Dai et al., 1998).

As reported in the mouse, PVT is among the targets of SCN neurons which express prokineticin 2, a secreted protein implicated in the regulation of biological rhythms and in the transfer of circadian information from the master clock to its targets (Zhang et al., 2009a,b). The SCN is the source of AVP, VIP, GRP fibers which innervate PVT (see Section 2.1). Patch-clamp recordings in rat brain slice preparations (see Section 5) indicate that such fibers are excitatory (Zhang et al., 2006a). Whole cell recordings in acute rat brain slices prepared during day or night (see Section 5) have also indicated the existence of glutamatergic and GABAergic SCN input to PVT, without significant day/night differences in the observed neuronal properties, thus implicating that the SCN projection to PVT is "hard wired" (Zhang et al., 2006b).

By means of multiple labeling approaches at the light and ultrastructural levels, axon terminals of SCN fibers were found to establish synaptic contacts on PVT neurons projecting to the amygdala (Peng and Bentivoglio, 2004). PVT projection neurons could also potentially convey circadian timing information from the SCN to the medial prefrontal cortex and nucleus accumbens (Fig. 3).

Photic input reaches indirectly PVT not only via the SCN, but also through input from the intergeniculate leaflet, as reported in the rat (Moore et al., 2000). In the so-called "extended circadian system", that includes numerous brain regions potentially involved in circadian rhythm regulation, PVT is the only thalamic cell group that receives a direct input from both the SCN and the intergeniculate leaflet (Morin, 2013). Interestingly, some retinal fibers also reach directly PVT, as well as the other thalamic midline nuclei and the intralaminar nuclei, as described in the marmoset (Cavalcante et al., 2005), and in the rodent rock cavy (Nascimento et al., 2008).

The SCN input to PVT is reciprocated by moderately dense PVT projections to the SCN (Moga and Moore, 1997; Moga et al., 1995; Vertes and Hoover, 2008). PVT efferents reach the entire SCN, being most numerous in the anterior and dorsal portions of the nucleus. Glutamate is released by PVT axon terminals in the SCN, and GABA co-release has also been reported in the rat (Alamilla and Aguilar-Roblero, 2010). However, as mentioned above (see Section 2), PVT does not contain GABAergic neurons in the rat, so that this finding remains to be verified.

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Another interesting aspect of the relationships of PVT with circadian timing regulation is represented by the concentration, in this nucleus, of melatonin receptors. Melatonin, "the neuroendocrine hand of the clock" (Stehle et al., 2003), is the hormone rhythmically secreted by the pineal gland, which has peak levels and is released during the night. Melatonin provides a humoral message to the SCN concerning the duration of darkness (Dibner et al., 2010; Golombek and Rosenstein, 2010; Stehle et al., 2003). Binding sites of high affinity melatonin receptors are very dense in PVT in different species (von Gall et al., 2003).

3.2. Clock gene expression

The existence of a number of possible circadian oscillators in the mammalian brain "challenges the omnipotence" of the SCN (Guilding and Piggins, 2007). PVT has not reached up to now the full dignity of a brain oscillator (Guilding and Piggins, 2007), although novel data on diurnal changes of the intrinsic activity of PVT neurons (see Section 5) should lead to a reconsideration of this aspect.

At the cellular level, the clock is provided by a network of clock genes, the transcription factors which maintain the rhythmic, circadian expression of their target genes (Buhr and Takahashi, 2013). When expression of the *Per1* clock gene was monitored in neural tissues cultured from rats carrying the *Per-luciferase* transgene, isolated PVT tissue was among the 14 brain areas (of the 27 examined) showing a rhythmic *Per1* transcript expression that peaked during the night, as in other areas except for the SCN where the peak was during the day (Abe et al., 2002).

Reports on clock gene expression in PVT *in vivo* are related to feeding behavior. Daily oscillation of the expression of PER1 and PER2 proteins was found in PVT in rats (Angeles-Castellanos et al., 2007; Mendoza et al., 2005) and mice (Feillet et al., 2008) entrained to the light/dark cycle, and the rhythmic expression of PER1 was maintained in rats kept under total darkness (Mendoza et al., 2005). PER1 rhythm of expression in PVT showed a phase shift at a palatable meal-time (Mendoza et al., 2005), and in rats entrained by daily restricted feeding schedules (Angeles-Castellanos et al., 2007). Oscillation of the expression of the clock gene *Cry1* and the clock-controlled gene *Dbp* have also been documented in the mouse PVT, where PER1, PER2, *Cry1* and *Dbp* rhythmic expression was affected by hypocaloric feeding (Feillet et al., 2008).

The functional impact of the daily rhythmic oscillation of the expression of clock genes in extra-SCN brain regions remains a key open question (Bonaconsa et al., 2013), which applies also to PVT neurons and the multiple circuits in which they are inserted.

3.3. Which kind of circadian timing information is processed in the paraventricular thalamic nucleus?

Although "it is likely that all SCN efferent projections carry circadian rhythm phase information to distal targets in other systems" (Morin, 2013), the functional role of circadian timing information in such distal targets is still unclear, and PVT is no exception.

In the hamster, lesions of the anterior part of PVT were not found to impair neuroendocrine response to short photoperiod, circadian rhythm of locomotor activity or entrainment to light of activity (Ebling et al., 1992). These findings favored the view that the anterior part of PVT "is not an essential component of the neural mechanisms responsible for circadian and photoperiod time measurement" (Ebling et al., 1992). Lesions also indicated that PVT is not critical in food anticipatory circadian rhythms (Landry et al., 2007). However, the data on clock gene expression in PVT mentioned above (see Section 3.2) indicate that PVT is sensitive to feeding cues, and suggest that the non-photic information conveyed by PVT efferents to the SCN could be involved in feeding entrainment of the circadian pacemaker (Angeles-Castellanos et al., 2007; Feillet et al., 2008). In addition, in the study of entrainment to light of the circadian rhythm of drinking behavior in the rat, lesions of the anterior PVT abolished the shift induced by light pulses, glutamate or electrical stimulation, pointing to a contribution of PVT to the entrainment of endogenous rhythms to light (Salazar-Juárez et al., 2002). Furthermore, PVT lesions in the blinded rat caused a period lengthening of the free-running circadian rhythm, with concentration of locomotor activity in the late subjective night, suggesting a participation of PVT in the control exerted by the SCN on the rest/activity rhythm (Moga and Moore, 2000).

Fos immunoreactivity induced in the posterior division of PVT by acute stress did not show significant differences between daytime and nighttime in the rat (Chastrette et al., 1991). Circadian regulatory functions of PVT could, however, manifest in relation to the role of this nucleus in the adaptation to chronic stress (Hsu et al., 2014; Fig. 3). Thus, in the rat, PVT appears to affect the core temperature rhythm and energy balance only in chronically stressed animals (Bhatnagar and Dallman, 1999).

3.4. The diencephalic heart of sleep/wake regulation

In the scalp-recorded electroencephalogram (EEG), wakefulness is characterized by activation of the cerebral cortex with low-voltage fast activity, high muscle tone and behavioral arousal. Sleep involves sequential stages, with alternating cycles of short periods of rapid eye movement (REM) sleep preceded by slow wave (non-REM) sleep, characterized by high-amplitude slow-frequency EEG activity, decreased muscle tone and behavioral quiescence. During REM sleep, EEG is desynchronized as in wakefulness, but, in contrast, there is a loss of postural muscle tone besides the characteristic eye movements (Brown et al., 2012; Pace-Shott and Hobson, 2002).

According to the two-process model of sleep regulation (Borbély, 1982; Daan et al., 1984), homeostatic and circadian factors are integrated: the sleep/wake-dependent homeostatic process leads to an exponential increase in sleepiness during wake; the sleep/wake-independent circadian process counteracts the increasing sleep propensity during wake, and controls the sleep–wake cycle. The integration between the increase in sleep pressure during wake and the circadian propensity to initiate sleep is critical not only for state-dependent behavior, but also for synaptic plasticity phenomena and cognitive functions, especially memory consolidation (e.g. Colavito et al., 2013; Diekelmann and Born, 2010; Hobson and Pace-Schott, 2002; Stickgold, 2005; Stickgold and Walker, 2013; Tononi and Cirelli, 2014).

Sleep and wake are regulated by a distributed neural network, with centers in the brain stem, diencephalon and basal forebrain (Brown et al., 2012; Datta and Maclean, 2007; Jones, 2005; Pace-Shott and Hobson, 2002). The multiple systems involved in wakefulness seem to show a redundancy, at variance with the neural substrate for active sleep generation. A key role is played by the hypothalamus: in the anterior hypothalamus, neurons of the ventrolateral preoptic area, which contain the inhibitory neurotransmitters GABA and galanin, inhibit wakefulness-related neurons; the preoptic area can in turn be inhibited by wake-active neurons, creating a bidirectional inhibition loop (Saper, 2013; Saper et al., 2005a).

During wakefulness, multiple neurotransmitter-characterized systems are activated, and reach the cortex through a relay in the thalamus or directly. Cholinergic neurons in the mesopontine tegmentum that project to the thalamus reach the cortex through the thalamocortical system. Noradrenergic neurons of the locus coeruleus, and serotonergic neurons of the dorsal raphe in the brainstem, as well as hypothalamic histaminergic neurons of the tuberomammillary nucleus, and orexin-containing neurons (see

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Section 3.5) are widely distributed upon the cortical mantle, besides their thalamic relays.

Sleep-related oscillatory activity and state-dependent gating of sensory information are operant in the thalamus (McCormick and Bal, 1994; Steriade et al., 1993; see also Section 5). Oscillations during slow-wave sleep are generated as the result of the interaction between the activity of excitatory thalamocortical neurons and corticothalamic neurons, and the inhibitory activity of Rt (Hobson and Pace-Schott, 2002; Steriade, 2005). Classical electrophysiological findings in the cat have demonstrated sleep/wake-related changes in neurons of the anterior intralaminar nuclei, with a prevalence of tonic firing during wakefulness and REM sleep, and of burst firing mode during slow-wave sleep (Steriade et al., 1993). Electrophysiological studies in the cat have also demonstrated a role of Rt as a pacemaker of thalamocortical activity, responsible for the generation of the oscillatory waves represented by sleep spindles (Steriade, 2005; Steriade et al., 1987).

All this wealth of data demonstrates that the thalamus and the hypothalamus are critical centers for sleep/wake control.

3.5. Orexinergic innervation of the thalamus

A breakthrough in the organization of activating systems and the regulation of wakefulness was represented by the discovery of new peptides by two groups in 1998, which named them orexin-A and orexin-B (the nomenclature we here adopted) focusing on their role in appetite (Sakurai et al., 1998) or hypocretin-1 and hypocretin-2 on the basis of their substantial amino acid identity with the gut hormone secretin (de Lecea et al., 1998). The orexins, synthetized by neurons located in the lateral and perifornical areas of the hypothalamus, and largely co-localized in the same neurons (Nixon and Smale, 2007), project widely to the brain and spinal cord (Peyron et al., 1998). Orexin-A and orexin-B are cleaved from the common precursor preproorexin, and bind to two G-protein coupled receptors. The orexin-1 receptor binds orexin-A; the orexin-2 receptor binds both orexin-A and orexin-B.

The discovery of orexins raised immediate attention, also due to the finding of impaired orexinergic signaling in the sleep disorder narcolepsy (see Brown et al., 2012; Sakurai, 2007). The orexinergic system has been implicated in the regulation of a variety of functions, so that the orexins have been recently defined as “multitasking neuropeptides” (Sakurai, 2014): feeding and energy homeostasis, reward, emotion, attention, arousal stability and state transition (de Lecea and Huerta, 2014; Sakurai, 2007; Sakurai and Mieda, 2011). Recent emphasis has been given to an overall key role of orexins in the motivational aspects of behavior (Mahler et al., 2014; Sakurai, 2014).

With the discovery of orexins and analyses of their projections, different gradients of density of orexinergic innervation in the brain have been pointed out. Thus, orexinergic fibers are densely distributed within the hypothalamus but spare the SCN; the innervation of the amygdala and the striatal complex is very sparse, with a slight prevalence in the shell of the nucleus accumbens (Baldo et al., 2003; Peyron et al., 1998; Schmitt et al., 2012; Fig. 3). Orexinergic fibers are sparsely and widely distributed upon the cerebral cortex (Peyron et al., 1998; Fig. 3). The prefrontal cortex could, however, represent a preferential target, as retrograde tracing in the rat indicated that innervation of the prefrontal cortex derives from about one-third of orexin neurons (Fadel et al., 2002).

In the thalamus, orexinergic fibers have a remarkably discrete distribution. This delineates the midline nuclei with lower density in the intralaminar nuclei, sparing the rest of the thalamus, in rodents (Kirouac et al., 2005; Peyron et al., 1998), as well as in other species, including the human thalamus (Moore et al., 2001). Orexinergic fibers are especially dense in PVT, as shown in the rat (Baldo et al., 2003; Kirouac et al., 2005), in the mouse (Fig. 2), in the hamster (McGranaghan and Piggins, 2001; Mintz et al., 2001), in the monkey (Hsu and Price, 2009), and in subterranean mammals, the African mole rats, which have a free-running circadian activity (Bhagwandin et al., 2011). In the laboratory rat, orexinergic innervation was found to be distributed throughout the anteroposterior extent of PVT, much denser than in the adjacent midline and anterior intralaminar nuclei and the habenulae (Peyron et al., 1998; Kirouac et al., 2005). Innervation of the dorsal thalamic midline was found to derive from neurons dispersed throughout the area containing orexinergic neurons (Kirouac et al., 2005). As shown in Fig. 2, orexinergic fibers arborize profusely in PVT reaching the ependymal surface, and contact calretinin-expressing PVT neurons. Both orexin receptors are expressed in PVT (Cluderay et al., 2002; Hervieu et al., 2001; Marcus et al., 2001).

Retrograde tract tracing combined with immunohistochemistry showed the convergence of orexinergic and CART-expressing fibers (see Section 2.1) on PVT neurons projecting to the shell of the nucleus accumbens (Parsons et al., 2006). CART peptides are implicated in food intake, stress and endocrine regulation (see Kirouac et al., 2006). The convergence of orexinergic and CART afferents on PVT neurons projecting to the nucleus accumbens points to a role of PVT in the transfer of arousal and homeostatic information into the limbic portion of the striatal complex.

Intracerebroventricular infusion of orexin-A and orexin-B increases Fos expression (see Section 4) in PVT (Date et al., 1999), and orexins exert an excitatory effect on PVT neurons *in vitro* (Section 5) through postsynaptic orexin-2 receptors (Huang et al., 2006; Ishibashi et al., 2005; Kolaj et al., 2007), as also reported in neurons of the central medial and rhomboid nuclei (Bayer et al., 2002).

From the functional point of view, the orexinergic innervation of the thalamic midline, and in particular of PVT, has been related to the different functional aspects subserved on one hand by the orexinergic system, and on the other hand by PVT neurons (Fig. 3). It has thus been proposed that PVT is a regulatory station of energy balance and arousal, integrating it with reward mechanisms (Kampe et al., 2009; Kelley et al., 2005; see Section 2.3). Glutamatergic PVT neurons projecting to the prefrontal cortex are strongly excited by orexins, and in particular orexin-B, an effect supposed to serve as a “state-dependent amplifier” for the effect of orexins on arousal (Huang et al., 2006).

The action of orexin in PVT has been implicated in the effects of nicotine on arousal and cognition and in nicotine addiction: peripheral nicotine administration increases Fos expression in orexin neurons projecting to PVT, as reported in the rat (Pasumarthi and Fadel, 2008), and increases of Fos expression in PVT neurons, as reported in the mouse (Dehkordi et al., 2014). Data in rat prefrontal cortical slices have shown that orexin and nicotine excite the same thalamocortical synapses (Lambe et al., 2005), pointing out a direct interaction of orexin and nicotine with thalamic midline terminals in the prefrontal cortex, besides their actions on PVT neurons. The effects of orexin and orexin signaling in PVT have also been implicated in alcohol addiction (Barson et al., 2014; Dayas et al., 2008).

Orexin-A administration into PVT in the rat increases dopamine levels in the nucleus accumbens (Choi et al., 2012) and inhibits locomotor activity (Choi et al., 2012; Li et al., 2009), suggesting that orexin release in the midline thalamus could limit locomor activity to enhance vigilance allowing the expression of other behaviors (Li et al., 2009). Endogenous orexin signaling in PVT mediates hedonic feeding responses in the rat (Choi et al., 2012). On the other hand, endogenous orexin release in PVT has been implicated in the regulation of anxiety level in the rat, as part of “an orexin-PVT emotional arousal system” (Li et al., 2010a; Fig. 3), and in negative emotional states, and in particular in the aversive effects of morphine withdrawal (Li et al., 2011), as also indicated by changes in emotional behavior after microinjections of orexins in PVT (Li

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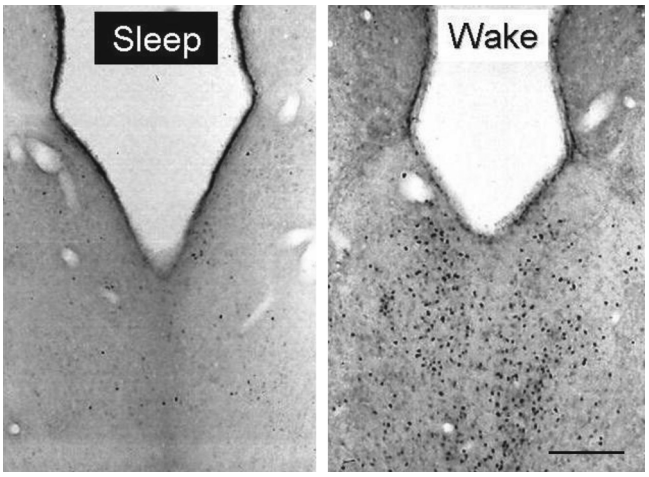

Fig. 4. Fos immunoreactivity (which labels the cell nuclei) in the posterior part of the paraventricular thalamic nucleus after a period of sleep and a period of wakefulness, as determined by electroencephalographic recording, in rats maintained under the light/dark cycle. Note the striking difference in Fos immunolabelling between the two states, with prominent expression during wakefulness, suppressed during sleep (images from the laboratory archival material). Scale bar: 100 μm.

et al., 2010b). Orexin actions in the posterior PVT have been related to repeated stress adaptation, preparing PVT neurons to the exposure to subsequent novel stressors (Heydendael et al., 2011). On the other hand, the responses to stressors obviously require vigilance and arousal, so that the orexinergic wiring of PVT could represent an important component of this integrative action of PVT neurons (Fig. 3).

4. Immediate early gene induction places the paraventricular thalamic nucleus on the sleep/wake stage

In nocturnal rodents the light phase of the light/dark cycle corresponds to the rest phase (and to the sleep phase when defined by EEG recording), and vice versa for the activity, wakefulness phase during darkness. Initial observations of the spontaneous variations of the expression of the immediate early gene *c-fos* during 24 h in light/dark conditions in the rat indicated that the level of this transcript increases at the lights-off time, remains high throughout nighttime and peaks at the end of the period of darkness to be then downregulated during the light period (Grassi-Zucconi et al., 1993). Increase of the protein product Fos was also reported in the rat brain after spontaneous wakefulness (Cirelli et al., 1993; Pompeiano et al., 1994). Spontaneous oscillation of *c-fos* expression with wake and sleep was found in mice (Basheer et al., 1997) and in the hibernating ground squirrel (O'Hara et al., 1997).

When examined after EEG recording, numerous Fos-immunoreactive cells were found in different brain regions and especially in the cerebral cortex after a period of wakefulness, with a dramatic decrease after a period of prevalent sleep (Grassi-Zucconi et al., 1994). A striking oscillation of Fos basal expression was consistently found in PVT (Peng et al., 1995; Fig. 4). In the thalamus, Fos was found to be increased also in the anterior intralaminar nuclei during spontaneous wake (Pompeiano et al., 1994). However, in our experimental series (Peng et al., 1995), labeling in the midline nuclei and in particular in PVT was a consistent feature during wake, whereas Fos labeling in anterior intralaminar domains was evident only after a period of sustained wake, when Fos-immunoreactive cells were very numerous in the brain, especially in the cerebral cortex. On the other hand, the number of Fos-immunoreactive cells in PVT increases with the duration of wakefulness, as shown in rats after sleep deprivation by gentle handling (Cirelli et al., 1995) or by the use of slowly rotating wheels (Semba et al., 2001).

In the rat, Fos spontaneous induction in PVT, as well as in the central medial nucleus, during the dark phase of the light/dark cycle was found to be in antiphase with Fos induction in the ventrolateral preoptic area (Novak and Nunez, 1998), the sleep-promoting hypothalamic cell group (see Section 3.4) in which Fos is induced during sleep (Sherin et al., 1996). In a diurnal species, the Nile grass rat, Fos expression in PVT was mostly correlated with the activity pattern, being highest in their morning activity bout, whereas no rhythm in Fos expression was found in the central medial nucleus, suggesting a stronger circadian modulation of PVT (Novak et al., 2000b). Altogether these data have shown in different species a correlation of activity and wakefulness with prominent upregulation of Fos expression in PVT among other brain regions, "erased" then by rest and sleep.

Immunohistochemistry combined with retrograde tract tracing revealed that PVT neurons which express Fos during spontaneous wake include cell populations projecting to the amygdala, concentrated in the anterior part of PVT, as well as cell subsets projecting to the nucleus accumbens which prevail in the posterior part of PVT (Peng et al., 1995). Whatever information is subserved by spontaneous Fos induction, its diurnal variation is, therefore, conveyed from PVT to limbic targets.

In our study on the wake-promoting agent Modafinil, Fos induction in PVT was not significantly higher in treated rats with respect to controls (Gozzi et al., 2012). However, the pattern of *c-fos* induction in the brain during wakefulness and arousal induced by psychostimulants varies, and different mechanisms of action of different arousal-promoting drugs could account for this variability (Cirelli and Tononi, 2000).

Fos induction during wake occurs in both excitatory and inhibitory neurons, as shown in the rat cerebral cortex (Bertini et al., 2002). In general, Fos is considered a marker of neuronal activity, but the threshold for Fos induction by specific stimuli varies among neuronal subsets (Herdegen and Leah, 1998). Induction of the c-*fos* gene, which has many downstream target genes, has been proposed to reflect synaptic plasticity rather than neuronal firing *per se*, and the significance of its oscillation during the sleep/wake cycle remains to be determined (Cirelli and Tononi, 2000).

The decrease of Fos expression with sleep (even after short periods of sleep) was ascribed to a cessation of Fos synthesis and/or the activation of a proteolytic pathways (Basheer et al., 1997). Whatever its biochemical mechanism, the spontaneous Fos induction in basal conditions in PVT neurons and other neuronal subsets is a

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molecular signature of wakefulness, and its suppression a molecular signature of sleep.

5. Intrinsic properties of paraventricular thalamic neurons reveal diurnal changes

Electrophysiological analyses have revealed that the information transfer and the modality of response of thalamocortical neurons to excitatory synaptic inputs depends on the arousal state of the organism. Two distinct modes of firing have been described: tonic firing, which consists in single action potentials, and burst firing, in which cells fire two to seven action potentials, thereby thalamic neurons are "bistable" (Jahnsen and Llinás, 1984a; McCarley et al., 1983). When the cell is depolarized by an outward current applied to the resting membrane potential, the cell responds with tonic firing, whereas a transient depolarization applied to a relatively negative (−65 mV) resting membrane potential results in a low threshold spike (LTS) that is crowned with one or more sodium dependent action potentials.

Tonic and burst firing coexist in the same neuron and depend on the state of voltage-dependent inward current (Crunelli et al., 2005; Jahnsen and Llinás, 1984b; Steriade, 2005). The two firing modes, confirmed in all major thalamic nuclear groups, correspond to distinct functional states and reflect the degree of the neuron responsiveness to external stimulation. Hyperpolarization and repetitive burst firing have been described during slow-wave sleep and some pathological conditions (such as absence epilepsy), whereas depolarization and a tonic single-spike firing mode have been observed during wakefulness (Llinás and Steriade, 2006; McCormick and Bal, 1994). However, thalamic bursting activity was recorded also during wakefulness as well as in periods of sensory processing, indicating that also this modality can provide an effective relay mode in the awake state (Fanselow et al., 2001; Reinagel et al., 1999).

In vitro patch-clamp studies confirmed that PVT neurons share such state-dependent firing behavior with other thalamic neurons and respond to intracellular current pulse either by tonic or burst firing depending on the cell intrinsic status at any given moment. In particular, after depolarization from resting membrane potential, PVT neurons respond with tonic firing, whereas at a relatively hyperpolarized membrane potential PVT neurons display LTS and bursts of action potentials (Zhang et al., 2006a).

As briefly mentioned above, the generation of fast action potentials in thalamocortical neurons depends both on the membrane conductances and on ionic currents (Jahnsen and Llinás, 1984b). PVT neurons display interesting and peculiar differences in the electric properties compared to the other thalamic cells in general and to midline thalamic neurons in particular (Kolaj et al., 2014a,b). Initial investigations showed that in PVT neurons the entry of Ca^{2+} ions through the low-voltage-activated (LVA) Ca^{2+} channels, that mediates burst firing, stimulates the release of Ca^{2+} from intracellular stores, demonstrating the association with Ca^{2+}-induced Ca^{2+} release (Richter et al., 2005). This also occurs in other thalamic midline neurons, but not in the majority of thalamocortical sensory relay nuclei. In PVT neurons, as in neurons of thalamic sensory relay nuclei, LVA Ca^{2+} channels are predominantly distributed on proximal dendrites, although Ca^{2+} responses are markedly heterogeneous in different dendrites of the same cell and even in different regions of individual dendrites (Richter et al., 2006).

Another interesting aspect of PVT neuronal excitability is membrane afterhyperpolarization, which is responsible for the rhythmic activity of PVT neurons and is mediated by unique types of K^+ channels. Slow afterhyperpolarization (sAHP) seems to play a unique role in PVT neurons, as it is absent in other thalamic neurons, such as ventrobasal or Rt neurons (Kolaj et al., 2014b; Zhang et al., 2010). Two kinds of sAHP can be observed in PVT neurons: LTS-induced sAHP and spike train-induced, or post-burst, sAHP. Post-burst sAHP is strongly dependent on the influx of Ca^{2+} ions, as demonstrated by its abolition following the application of tetrodotoxin blocking voltage-dependent Na^{2+} channels and thereby the influx of Ca^{2+}. Under intense burst firing, a role for potassium-activated Na channels (KNa) was also reported (Zhang et al., 2010). This behavior accounts for 35% of the overall sAHP observed in PVT neurons. On the other hand, a subpopulation of PVT neurons exhibits Ca^{2+}-dependent long-duration LTS-induced sAHP, mediated by T-type Ca^{2+} channels, which is insensitive to the application of tetrodotoxin and cadmium and unaffected by apamin, but is blocked by Ni^{2+} (Zhang et al., 2009a,b).

A recent report (Wong et al., 2013) has revealed other differences of the tonic firing behavior of PVT neurons compared to that of other thalamic neurons, in particular due to the propensity of PVT neurons to enter a depolarization block, thus leading to termination of tonic firing. Neurons in PVT are unable to fire a sustained train of action potentials above 120 pA, that would elicit tonic firing in other thalamic neurons. Therefore, when stimulated by higher current, PVT neurons enter a long-lasting depolarized state and plateau, with the contribution of all three subtypes of high-threshold voltage-gated calcium channels. This could serve a filtering adaptive function, and the narrow dynamic range of PVT neurons could be a key feature of their integrative properties (Wong et al., 2013).

Importantly and of special interest in the present context, PVT seems to be the unique portion of the thalamus where these properties appear to change depending on the circadian time of the day (Fig. 5). Such diurnal variation was described comparing coronal slices prepared from rats during day and night. When whole cell patch-clamp recording of anterior PVT neurons was performed in slices prepared during the periods of light or darkness, marked diurnal variations were found. PVT neurons showed highest activity during the hours of darkness, corresponding to the period of subjective vigilance (Kolaj et al., 2012). The majority of neurons recorded during the subjective day (rest) phase were silent, whereas most of the neurons recorded during the subjective night (active) period showed spontaneous activity, both as tonic and burst firing (Kolaj et al., 2012). Furthermore, neurons at night were more depolarized and exhibited lower potassium conductances and decreased resting membrane potentials (Fig. 5A and B). Accordingly, the amplitude of T-type low-voltage-activated Ca^{2+} currents was enhanced in slices from the night period and RT-PCR analysis revealed an increase for two T-type Ca^{2+} channel isoforms ($Ca_v3.1$ and $Ca_v3.3$) in tissue samples from anterior PVT in the dark phase (Kolaj et al., 2012). Patch-clamp recording in slices from transgenic mice indicated that the thalamic T-type $Ca_v3.1$ Ca^{2+} channel expression in midline and intralaminar nuclei is important to block transmission of arousal signals through the thalamus and for sleep stabilization (Anderson et al., 2005). When hyperpolarization-activated cation current (I_H) was inhibited, PVT neurons from the night period were more affected, showing a significantly larger hyperpolarization than neurons in the day period, in the absence of differences in mRNA expression of individual I_H-type channel isoforms (Kolaj et al., 2012).

All the changes described above influence both spontaneous and induced firing patterns, and differences between day and night were found also in this respect. When the membrane potential was changed to −50 mV, PVT neurons from both day and night exhibited tonic firing, whereas at −70 mV they were all silent. However, when the membrane potential was stepped to −60 mV only night neurons responded with burst firing (Kolaj et al., 2012; Fig. 5c). Following membrane hyperpolarization, night PVT neurons responded with an increase of the number of bursts following LTS, while the neurons recorded in the light period showed only a single LTS (Kolaj et al., 2012; Fig. 5b and d).

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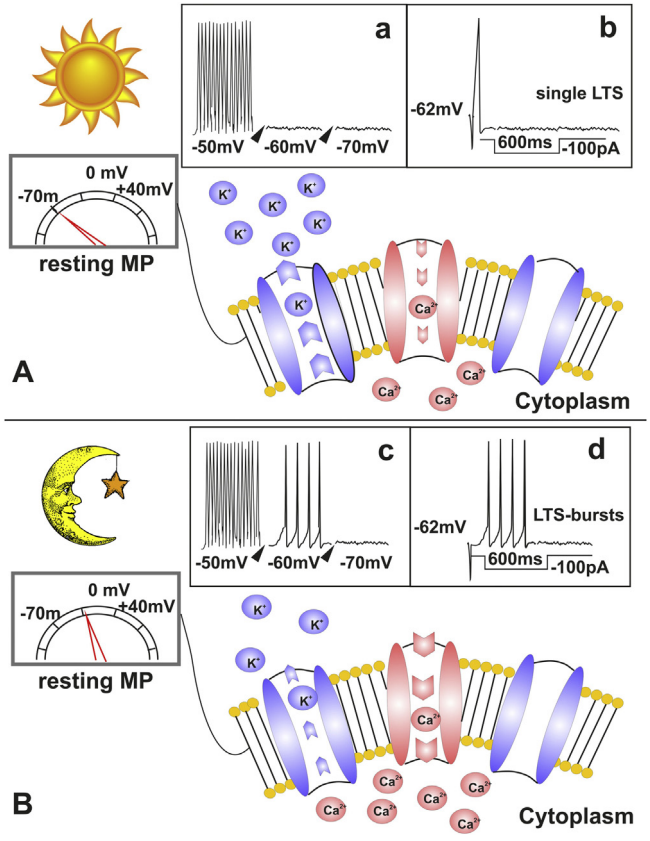

Fig. 5. Intrinsic diurnal properties and activity patterns of neurons of the paraventricular thalamic nucleus (PVT). The drawing shows schematically a segment of the neuron membrane. Anterior PVT neurons during the night period show more depolarized resting membrane potential (MP) (B), and lower resting conductances mainly due to lower K^+ currents and larger amplitude T-type-low-voltage activated Ca^{2+} currents with respect to neurons recorded during the day period (A). At −70 mV, neurons recorded both during the day and the night period are silent, whereas when the MP is changed at −50 mV they display tonic firing (a and c). When the MP is stepped to −60 mV, only night neurons respond with tonic firing. Following membrane hyperpolarization, night PVT neurons respond with an increase of the number of bursts following a low threshold spike (LTS), while the neurons recorded in the light period only show a single LTS (b and d).
Adapted from Kolaj et al. (2014a).

As for the action of orexins (see Section 3.5), the vast majority of PVT neurons responded to orexin-A and orexin-B with tetrodotoxin-resistant membrane depolarization mediated by postsynaptic receptors (Kolaj et al., 2007), indicating that orexins can modulate the state-dependent properties of PVT neurons. However, concerning the effect of orexins (Doroshenko and Renaud, 2009; Kolaj et al., 2007), and AVP (Zhang et al., 2006b; see Section 3.1) on the excitability of PVT neurons, it remains to be clarified whether and how the diurnal changes described above are the consequence of the modulation of these two peptides, since patch-clamp recordings have been hitherto performed only on rat slices prepared during the light period.

6. Concluding remarks: the funnel of information on state-dependent behavior into the limbic system

At the center of the brain and at the center of the thalamus, routing a remarkable array of brain stem and hypothalamic inputs into cortical and subcortical limbic and limbic-related centers, the thalamic midline emerges as unique neural crossroad. Funneling information into the limbic system appears its main task. In the dorsal thalamic midline, this information includes circadian timing, arousal, wakefulness and sleep states.

In a strategic, though often underscored, position in the non-image forming visual system, PVT receives photic information directly from the retina as well as from retinal-recipient circadian timing centers (the SCN and the intergeniculate leaflet). The solar day affects directly not only biological rhythms, but also reward, mood, affect, emotions, cognition (Gaggioni et al., 2014; LeGates et al., 2014). As reviewed above, a wealth of data involves PVT in these mechanisms (Fig. 3). Dysregulation of these processes is implicated in depression and affective disorders (LeGates et al., 2014), in which the role of the thalamic midline deserves to be investigated.

The thalamus and the hypothalamus are protagonists of knowledge accumulated over decades of the neural control of sleep and wakefulness. As discussed above, the key role of the thalamocortical system in sleep/wake regulation resides in the activation and deactivation of the cerebral cortex and the role of Rt as pacemaker of thalamocortical neurons. The key role of the hypothalamus resides in circadian timekeeping, sleep-promoting and wake-promoting hypothalamic centers. But where do thalamic and hypothalamic mechanisms interact? The dorsal thalamic midline, with PVT running the show, could represent such a meeting point for the integration of these diencephalic mechanisms.

Importantly, the neurons of the dorsal thalamic midline appear to provide a unique downstream contribution to the limbic system by the transfer of state-dependent behavioral information, for the temporal architecture of many physiological processes, for the response to stress, and for the emotional, affective dimension of cognitive tasks.

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